Ethical Review of In Silico Methodologies

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7.1 Introduction

Before any experimental study can be conducted on humans, the study design must be approved by an independent body responsible for protecting the safety, well-being and rights of the human subjects involved in the experimentation. These bodies are called Independent Ethics Committees in Europe and Institutional Review Boards in the USA; hereinafter, we will use the acronym IEC/IRB to indicate them.

Existing regulatory, legal and ethical frameworks for clinical trials were developed because of well-established medical research practices involving human subjects. Rules were set to protect human research subjects from hazards. By contrast, in silico medical

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research relies on computational resources and data—using patient data to generate and validate computer models, which will be used to predict the necessary evidence.

7.2 Short Overview of Ethical Review in Clinical Trials

Research involving humans originated in a dark past, where human rights, safety and well-being were disregarded. And that past is not necessarily so remote (see, for example, the Tuskegee Study of Untreated Syphilis in the Negro Male[1]). With the progressive adoption of the Declaration of Helsinki and the establishment of the Good Clinical Practice[2] (GCP), Applicants/Sponsors and Investigators are required to ensure the proper conduct of the clinical trials.

Ethical aspects of any clinical trials are ensured by IEC/IRBs. These entities, which are either local or central, aim to ensure the safety, rights, and well-being of all subjects, whether healthy volunteers or patients, enrolled in any clinical experimentation. Although rules were originally defined for trials on medicinal products,[3] any trial involving experimental interventions (e.g., for surgical procedures or medical devices) must be submitted to IEC/IRBs before starting it. Also prospective and retrospective observational studies are submitted to IEC/IRBs to assess risks from additional diagnostic procedures, data protection, and the relevance of the research question.

IEC/IRBs review clinical protocol and the corresponding amendments, the written information on aims, procedures, and rights to be provided to subjects, and the relevant written informed consent forms. They also oversee the enrolment process, including procedures, compensation payments (when appropriate), insurance coverage, the Investigator's qualifications, etc. IEC/IRBs are therefore involved before, during, and after the clinical trial.

7.3 The Ethical Benefits of In Silico Methodologies

In silico methodologies aim to refine, reduce, and replace experimental studies conducted in vitro, ex vivo, or in vivo on animals or humans and provide evidence on medical products' safety, efficacy, and performance.

If we focus on in silico methodologies aimed to refine, reduce, and replace human experimentation, several potential ethical benefits can be associated with these new technologies.

[1] Https://en.wikipedia.org/wiki/tuskegee_syphilis_study.

[2] https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice.

[3] https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-536 2014_en.

7.3.1 Refinement

Refining human experimentation means reducing the risks to which the enrolled subjects are exposed and increasing the benefit/risk ratio of the experimentation. This means maximising the regulatory utility of the information obtained by exposing the enrolled subjects to such risks. In silico methodologies have been proposed to stratify patients better, improving the inclusion and exclusion strategies. This may produce ethical benefits when it helps to identify subjects at higher risk of adverse effects. Where this does not bias the conclusions of the study, such patients can be excluded; alternatively, their identification allows the adoption of measures to mitigate the risk, such as additional monitoring. In some cases, in silico methodologies can also directly reduce the risk for enrolled subjects. For example, studies in cardiology that require an invasive fractional flow reserve (FFR) measurement can now be conducted using CT-based virtual FFR models that provide a non-invasive estimate of the FFR for each subject enrolled.

7.3.2 Reduction

When an in silico methodology can reduce the number of subjects who need to be enrolled, and thus the number of persons who are exposed to the risks that the study involves, this represents a direct ethical benefit, according to the 6th principle of the Declaration of Helsinki: "*In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests*". The most obvious examples are in silico-augmented clinical trials, where virtual and physical patients are combined (Haddad et al., 2017). Other examples are those cases where the primary outcome is not easily observable, and thus a surrogate biomarker is used to measure response or efficacy. In studies on new drugs to prevent fragility bone fractures caused by osteoporosis, areal bone mineral density is frequently used as a surrogate of the fracture endpoint. A CT-based digital twin can predict the absolute risk of fracture for each patient enrolled; because this predicted quantity has much higher discriminant power, the number of patients enrolled in the clinical studies to achieve statistical power is much smaller (Viceconti & Dall'Ara, 2019).

7.3.3 Replacement

The complete replacement of human experimentation is currently not considered an option. However, there are several cases where human experimentation is impossible and others where a partial replacement might be an option. Human experimentation is impossible, for example, in assessing the MRI safety of implantable devices (e.g., heating of the device due to high-frequency electromagnetic pulses); here in silico methodologies

may provide evidence more reliable than animal experiments can provide (Baretta et al., 2020). Scenarios of partial replacement are those where, for example, the digital twin of the subjects enrolled could be used to form a placebo arm in studies where the placebo is considered unethical. Also, in silico methodologies can reduce the numerosity of a clinical required to achieve statistical significance (Haddad et al., 2017). The last scenario where in silico methodology may introduce ethical benefits is in studies where, for several reasons, the necessary diversity (of ethnicity, gender, age, physical conditions, etc.) is difficult to achieve with the necessary statistical relevance. In silico-augmented clinical trials could be designed not to increase the study's statistical power but to make it more representative by including tailored virtual patients of such underrepresented sub-groups.

7.4 The Ethical Review of Studies Involving In Silico Methodologies

When assessing a medical product involves in silico methodologies, are there special attentions that the IEC/IRB need to have in their reviews? To be answered, this general question must be articulated into more specific questions.

What is the role of the IEC/IRB when in silico methodologies are used to refine (i.e., to improve rather than to reduce or replace) human studies? We believe that the IEC/IRB is responsible for evaluating if a proper risk analysis has been conducted as part of the in silico methodology implementation and if this in silico approach reduces the risks for the subjects enrolled in the clinical trial or helped mitigate the adverse effects in case such risks materialise. In other words, the IEC/IRB needs to evaluate the ethical impact of in silico methodologies as they do for any other study methodology. However, this raises an issue of expertise in the current composition of IEC/IRB: such evaluation for in silico methodologies may require expertise rarely present in a typical IEC/IRB. In a time where studies involving in silico methodologies may still be a rarity, IEC/IRB may circumvent this problem by collecting, in such cases, the opinion of external experts to inform their own decisions. Still, it is reasonable to expect the inclusion of technology experts in IEC/IRB in the long run. Submissions to the IEC/IRB should be extended to include also the technical information necessary to evaluate such in silico methodologies.

If in silico methodologies are used to reduce the number of subjects enrolled in human studies, we do not see any significant change in how the IEC/IRB operates. In this case, all the concerns are on the reliability of a study's evidence, which concerns the regulatory bodies, not the IEC/IRB. Any means that can reduce the number of subjects enrolled without impacting the statistical relevance of the study should be seen positively from an ethical point of view.

The case where in silico methodologies replace human experimentation is the most complex.

The first question is: when a study involves only in silico methodologies (for example, in full replacement scenarios), is the IEC/IRB review necessary, considering no human subjects are involved in the study? We believe the answer is no, with one notable exception. IEC/IRBs ensure the safety of human subjects involved in the study; if no human subject is involved, there is no need for the IEC/IRB review. The only exception is when we need to use clinical data to design, inform, or validate the in silico methodology. In this case, the IEC/IRB review is required to ensure that the patient's data is treated according to the laws and the ethical principles that regulate these aspects. Frequently the clinical data to be used in the modelling activities are not collected on purpose; this poses the complex issue of re-using clinical data collected for clinical purposes or for research purposes different from the scope of the current study and whether an additional informed consent of the patients originally involved may be required. Because of its importance, this topic is discussed in greater detail below in a dedicated section.

But as we explained before, the replacement is only partial in some cases. And this frequently occurs when a portion of the study poses ethical problems (e.g., placebo, children, rare diseases). We suggest that such studies should first be subject to a regulatory advice procedure. The regulatory opinion on the appropriateness of the study design,[4] including the partial replacement of some human experimentation using in silico methodologies, should be acquired by the IEC/IRB, which would focus its evaluation of the ethical implications of the specific implementation of the study design, relying on the regulatory opinion for what matter the reliability of the evidence such study will produce. However, in this case, as in the previous one, the ethical evaluation will be difficult without the involvement of some technology experts. What we wrote before for the refinement scenario is also valid here: while initially, the IEC/IRB may rely on the opinions of external experts, in the long run, it is reasonable to expect the inclusion of technology experts in IEC/IRB.

7.5 Data Protection

With real-world data increasing, it is tempting to use them to build and validate computational models. In addition, digital twins in healthcare are informed by the clinical data of individual patients. For such applications, developers must account for data protection laws such as, for example, the European General Data Protection Regulation[5] (GDPR) or the USA Health Insurance Portability and Accountability Act[6] (HIPAA).

[4] As explained in Chap. 6, the regulatory pathways for in silico methodologies are only partially defined and tend to differ between USA and Europe.

[5] Https://gdpr.eu/.

[6] https://aspe.hhs.gov/reports/health-insurance-portability-accountability-act-1996.

An additional complexity for European developers is that the GDPR did acknowledge that the secondary use of clinical data for research purposes could justify some derogation but made no detailed provisions, leaving the member states to define the specific legislation. This has led to a very complex situation, where each country member of the European Union has different legislation. The main problem is not that of privacy (in most cases, the clinical data used in in silico methodologies are irreversibly anonymised) but rather that of data ownership. The European GDPR states clearly that the clinical data are owned by the patient, and the clinical institution where the data were generated is allowed to treat this data only for the necessary provision of care. Any secondary use must be explicitly authorised by the patient, the data owner, with informed consent. The point of debate is the granularity of such consent. The orientation of some privacy authorities in EU member states is that consent is given for each research project; thus, if the Investigator plans to reuse the clinical data for another research, he or she needs to collect new informed consent from each patient.

The recent EU Data Governance Act promises to solve this problem. This new EU-wide regulation, which will enter into force in September 2023, provides rules and safeguards to facilitate the re-use of data whenever possible. The main mechanism is that of *data altruism. Data altruism* is about individuals and companies giving their consent or permission to make available data that they generate—voluntarily and without reward—to be used in the public interest.

7.6 Credibility Assessment in the IEC/IRB Review

In most cases, the IEC/IRB is not called to directly evaluate the evidence of the credibility of the in silico methodologies. When the study results are to be used as part of a regulatory submission for marketing authorisation, it is usually expected that before using an in silico methodology for a specific context of use, a qualification opinion on such use needs to be obtained by a regulatory agency. In such a case, the qualification opinion should be attached to the IEC/IRB submission. It should be noted that while in the USA, the FDA can provide pathways for the qualification of in silico methodologies for medical devices and drugs development tools, in the EU, such qualification pathway is available only for drug development tools.

However, it could be a good practice to include any evidence of credibility available in the IEC/IRB submission. For example, if the credibility of the in silico methodology has been assessed using the ASME VV-40:2018 technical standards, the result summary of this assessment should be included in the submission.

7.7 Essential Good Simulation Practice Recommendations

In silico methodologies offer several potential ethical benefits:

- Refining human experimentation means reducing the risks to which the enrolled subjects are exposed but also increasing the benefit/risk ratio of the experimentation, maximising the regulatory utility of the information obtained by exposing the enrolled subjects to such risks.
- When an in silico methodology can reduce the number of subjects who need to be enrolled, and thus the number of persons exposed to the study's risks, this represents a direct ethical benefit.
- In silico methodologies can provide an ethical alternative where human experimentation is unethical.
- In silico methodologies can help in including in clinical studies the necessary diversity (e.g., of ethnicity, gender, age, physical conditions) that, for any reason, might be difficult to achieve experimentally.
- IEC/IRB should evaluate the ethical impact of in silico methodologies as they do for any other study methodology. With two special cases, both related to its use to replace human experimentation:

  - For studies where the in silico methodologies are used to partially replace human experimentation, the ethical review of the study by the IEC/IRB is necessary. Still, it should be based on the regulatory qualification opinion on the in silico methodology.
  - On the contrary, for studies that involve only in silico methodologies and no human experimentation, the IEC/IRB review is not necessary, with the notable exception of the ethical management of clinical data to design, inform, or validate the in silico methodology.

- To properly assess the ethical implications of in silico methodologies, IEC/IRB also need technical expertise. Initially, the IEC/IRB may rely on the opinions of external experts. Still, in the long run, it is reasonable to expect the inclusion of technology experts in the IEC/IRB.

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